Can an Aspirin a Day Keep the Colorectal Cancer Away?

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Colorectal cancer (CRC) is a major health concern. The progression of normal mucosa through adenoma to overt adenocarcinomas span over more than a decade. It provides a window of opportunities for early detection as well as the use of chemopreventive agents such as aspirin. Indeed, CRC can be prevented in up to 80-90% of the cases providing that physicians and patients compliance with current preventive strategies is high. Epidemiological and clinical randomised studies have clearly demonstrated an association between increasing aspirin use and incidence, prevalence and mortality from CRC. Although the evidence supporting the effect of aspirin on colorectal adenomas (CRA) and CRC prevention is consistent, a greater understanding of its mode of action is still needed. Incorporating CRC and CRA benefits into ischemic heart disease (IHD) and Alzheimer disease risk scores would be particularly useful for determining the benefit-to-risk ratio for aspirin use in borderline cases. For instance, patients with a borderline annual IHD risk, around 0.7-1.4%, but with a high risk for CRC may still benefit from aspirin usage. (Intest Res 2012;10:229-234)

Key Words: Colorectal Cancer; Cardiovascular Diseases; Alzheimer Disease; Cox 2 Inhibitor; Aspirin

INTRODUCTION

Cancer prevention is a major goal for healthcare providers, which is not surprising given that nearly 8 million causalities are attributable to cancer each year. Colorectal cancer (CRC) is a major health concern with 1.2 million new cases expected in 2012, resulting in over 600,000 deaths.¹ CRC carcinogenesis is a multi-step process that spans over two decades, providing a window of opportunities for effective interventions. CRC can be prevented by life style modification and screening programs in up to 80-90% of the cases only if physicians and patients compliance with current preventive strategies is much higher.²-⁵ The number of deaths due to CRC remains alarming high, and makes CRC prevention a paramount.

Efforts to improve the dismal outcome of CRC have focused on the potential role of non-invasive agents with chemopreventive activity. This concept is appealing and is finding a growing and enthusiastic audience in medical and scientific communities as well as among the public. Chemoprevention agents include polyphenols, isoflavones, curcumin, selenium, lycopene, vitamin D and its’ derivatives, hormone replacement therapy, folate, calcium and difluoromethylornithine. However, in the best case scenario, the preventive measures were able to prevent the disease by 15-20%. NSAIDs may seem to be more promising as they have been shown to reduce CRC incidence, prevalence and associated mortality irrespective of age, gender and study design.⁶ An analysis of 69 epidemiological (prospective, retrospective, cohort and case-control) studies revealed that in 67 of them, regular use of NSAIDs, aspirin, or the cyclooxygenase (COX)-2 inhibitors reduced the risk of colorectal neoplasia (Fig. 1). Much of their efficacy and toxicity has been attributed to their potent inhibition of COX enzymes.

In the benefit/risk evaluation we need agents of a considerable proven efficacy with low toxicity. The balance between benefit and harm should always be discussed with the patients in a clear way, taking into
consideration other diseases, and in particular ischemic heart disease (IHD). Subjects are likely to be more adherent to prescribed regimens if they aim to prevent cardiovascular disease (CVD) and Alzheimer disease (AD) at the same time with the same drug. Aspirin might be that magic bullet.

Aspirin was first synthesized more than a century ago. Many of its benefits, are still being discovered. Today aspirin is not only used to relieve pain but also as preventive therapy for CVD.

In the setting of CRC several cohort and case-control studies have confirmed the protective effect of aspirin. Chan et al. showed that 14 aspirin tablets per week reduces the incidence of CRC by up to 70% (relative risk [RR]=0.30, 95% confidence interval [CI] 0.11-0.81). In a prospective cohort study of 74,250 women, aspirin over 20 years reduced the risk of CRC by 35% (RR=0.65, 95% CI 0.45-0.94). Similar findings have been reported in other randomised controlled trials.

It is interesting that aspirin reduces the incidence of proximal CRC (hazard ratio [HR]=0.67, 95% CI 0.51-0.87). In a recent published study in over 300,000 subjects, the risk of distal and rectal cancer was reduced by only 16% (HR=0.84, 95% CI 0.71-0.99), and 24% (HR=0.76, 95% CI 0.64-0.90) respectively. Similar results were obtained in a meta-analysis of five randomised trials, with 55% risk reduction in the proximal colon (HR=0.45, 95% CI 0.28-0.74), with a slight non significant reduction in the distal colon (HR=1.10, 95% CI 0.73-1.64) or slightly, non significant, decrease of cancer in the rectum (HR=0.90, 95% CI 0.63-1.30).

The dose of aspirin and survival following a diagnosis of CRC is important, as was shown in a very large cohort study of 662,424 adults. A metaanalysis of four randomised trials (n=14,033) showed that CRC mortality was reduced by 34% (RR=0.66, 95% CI 0.51-0.85) over a follow-up period of 20-year. In another study, in 830 CRC patients, Fuchs et al. found that aspirin use was found to reduce CRC death by 48% (HR=0.52, 95% CI 0.19-1.46).

Aspirin is effective not only in decreasing the incidence and mortality from CRC but it can also prevent the disease. In a recent paper Burn et al. has clearly demonstrated that aspirin can decrease, by 38% (HR=0.62, 95% CI 0.41-0.96), the first cancer in 667 Lynch syndrome carriers. Consistent with studies in the sporadic setting, the protective effect of aspirin was linked to the duration of treatment; the odds ratio (OR) was 0.90 (<24 months of aspirin treatment) compared with 0.50 (>24 months of aspirin treatment). There are at least four randomised trials illustrating that aspirin is effective in the prevention of recurrent adenomas. The inhibitory effect is in particular effective in preventing the recurrence of advanced adenomas. A pooled analysis of these trials, in nearly 3,000 subjects showed that allocation to aspirin, over a median of 33-month period, reduced the risk of all adenomas by 17% (RR=0.83, 95% CI 0.72-0.96) and that of advanced adenomas by 28% (RR=0.72, 95% CI 0.57-0.90).

THE ANTI-NEOPLASTIC EFFECTS OF ASPIRIN

There are three isoforms of the COX enzyme. COX-1 is involved in platelet aggregation. Inhibition of COX-1-generated thromboxane A$_2$ (TXA$_2$) by low-dose aspirin is a key mechanism in the prevention of vascular damage. TXA$_2$ has also been shown to be involved in tumour metastasis and angiogenesis, and inhibition of TXA$_2$ synthase can reduce these effects. COX-2 is generated in response to hormones, cytokines and tu-
mour promoters, and COX-2-derived PGE₂ is the major prostaglandin found in many tumours. High level of COX-2 expression is seen in ~50% of CRAs and 80-90% of CRCs. COX-3, a splice variant of the COX-1 gene, has been discovered in the last decade, but its function is not yet known.

The relationship between COX-2 expression and aspirin use is important. In a study of 1,279 subjects, aspirin use was associated with a reduced risk of CRC and overall mortality in COX-positive primary cancers (n=314) (adjusted HR=0.39, 95% CI 0.20-0.76) as compared to COX-negative primary cancers (n=145) (adjusted HR=1.22, 95% CI 0.36-4.18). In another study, the effect of aspirin on survival of COX-2 positive as compared with COX-2 negative tumours was significant (p=0.04), with a HR 0.62 (95% CI 0.42-0.93) and 1.05 (95% CI 0.55-2.02) for COX-2-positive and negative primary cancers. The effect was also related to the dose and duration of aspirin. The multivariate RR of COX-2-positive and negative CRC was 0.38 and 0.60 in those who had taken on average two aspirin tablets per day, and 0.55 and 0.66, respectively, with over 20 years of regular aspirin use.

The overall scenario is far from being resolved, e.g., what is the effect of aspirin in left-sided COX 2 expressing CRC? It demands a better understanding of the effect of aspirin on non-COX-related pathways (Table 1). Non-COX targets of aspirin are most probably important in light of a recent paper reporting the protective effects of aspirin in hereditary non-polyposis colorectal cancer (HNPPC) patients that COX-2 is express in only 43% as compared to 92% of the cases in sporadic CRC.

### Table 1. The Effects of Aspirin on COX-independent Mechanisms

| Effects of aspirin on microsatellite instability |
| Induction of apoptosis |
| Effect on the Wnt/β-catenin pathway |
| Inhibition of angiogenesis |
| Modulation of NFκB |
| Inhibition of polyamine synthesis |
| Increase the expression of DNA mismatch repair proteins |
| Inhibition of sphingosine-1-phosphate |

#### DOSE AND DURATION CONSIDERATIONS

The minimally effective dose of aspirin required to exert anti-neoplastic effects has yet to be determined. It seems as if low cardioprotective dose of 75-100 mg/day is sufficient, providing that the drug is taken for at least 5 years. In a meta-analysis of randomised trials of aspirin, low-doses (75-300 mg/day) were associated with a 40% reduction in the long-term risk of CRC-related mortality, similarly to the 28% reduction seen in subjects consuming high doses (500-1,200 mg/day) of aspirin. And at the same time Chan et al., in a large epidemiological study, consisting of nearly 50,000 males, with a mean follow-up of 18 years, showed that the RR of CRC was higher in patients who used 14 aspirin tablets per week as compared to one tablet per week (RR=0.3 vs. 0.94). It implies that most probably the interval of taking the drug is more important than the strength of the dose. Taken together, low-dose aspirin taken regularly over several years is associated with a reduction in CRC incidence and mortality.

#### ASPIRIN USE IN SUBJECTS AT RISK OF CRC, AD AND CVD

Aspirin may play a major role in the prevention of IHD (Table 2), CRC (Table 3) and AD (Fig. 2), which are the three major health catastrophes in the third millennium. However, utilising the benefits of aspirin in prevention of such diseases must be weighed against the potential for any risks such as gastrointestinal bleeding. This is the principle of the cornerstone of medicine from its birth: primum non nocere. Optimising the benefit-to-risk threshold for aspirin use is essential for the effective management of any patient including its potential role in novel areas such as CRC prevention.

The use of methods of chemoprevention is of greatest importance for treating individuals which have a hereditary predisposition to CRC, e.g., familial adenomatous polyposis (FAP) and HNPCC subjects who have a life time risk to develop CRC of 100% and 65-85% respectively. The J-FAPP II trial, a double-blind, randomised, controlled clinical study will provide the answer regarding the risk/benefit of low-dose aspirin (100 mg/day) in Japanese patients. The CAPP2 trial...
An algorithm illustrating the use of aspirin in patients at risk of CRC, IHD and Alzheimer disease. IHD, ischemic heart disease; CRC, colorectal cancer; FAP, familial adenomatous polyposis. *FAP, Lynch syndrome, MYH polyposis. \(^\dagger\) Strong family history with early onset or carriers of mutations for Alzheimer disease.

**Table 2.** Number of Patients, with Risk for Ischemic Heart Disease (IHD) That are Needed to Be Treated with Aspirin for 10 Years in Order to Avoid One Case of IHD

<table>
<thead>
<tr>
<th>10-year risk of IHD (%)</th>
<th>Required number of subjects</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>133</td>
</tr>
<tr>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td>15</td>
<td>44</td>
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</table>

**Table 3.** Number of Patients Aged 50 Years Needed to Treat with Aspirin over a Period of 10–20 Years to Avoid One Case of Colorectal Carcinoma

<table>
<thead>
<tr>
<th>Required number of subjects</th>
<th>10 years</th>
<th>15 years</th>
<th>20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td>235</td>
<td>125</td>
<td>90</td>
</tr>
<tr>
<td>High risk</td>
<td>57</td>
<td>36</td>
<td>28</td>
</tr>
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reported a \(\sim 60\%\) reduction of CRC among 1,000 subjects with Lynch syndrome. The effect became apparent after five years in the trial and in those who took 600 mg aspirin daily for at least two years.\(^12\)

It is more important to identify patients with CRC risk factors in the general population. Age, gender, smoking, body mass index, diabetes and alcohol consumption are significant predictors of CRC (Tables 2, 3). Such a score was developed using a cohort of 21,581 US males who participated in the Physician’s Health Study over a 20-year follow-up period,\(^31\) we add to this scores polymorphisms in the CD24 and APC genes.

**SUMMARY**

CRC accounts for a significant proportion of cancer deaths worldwide. There is an urgent need for preventive strategies. There is strong evidence to support the notion that aspirin prevent adenoma recurrence, reduces the incidence of CRC and most importantly is
associated with lower mortality. The effect is mainly COX-2 expressing tumors and in the right colon, and if taken for a long period of time. Aspirin may be used as an adjuvant therapy. In one study it reduced CRC death by almost half.\textsuperscript{16} Although the evidence supporting the effect of aspirin on CRA and CRC prevention is consistent, a greater understanding of its mode of action, particularly with respect to its effect on COX-2 and non-COX-2 expressing cancers is required in order to clarify any issues regarding dose and treatment duration. Most probably aspirin chemoprevention should be used in conjunction with periodic screening colonoscopy\textsuperscript{34} or sigmoidoscopy.\textsuperscript{35,36}

The ideal chemopreventive agent is one that has proven to be effective, has a convenient dosing schedule, is inexpensive and causes minimal side effects or shows a low but acceptable toxicity profile in high-risk populations. Aspirin answers all of these criteria.

Obviously, the entire picture should be put in place, e.g., personalised medicine. The benefit-to-risk balance of aspirin for cancer prevention in conjunction with its well-established benefits in vascular disease, as well as its potential positive effects in subjects at high risk for AD make it an attractive candidate for reducing overall morbidity and mortality.

**REFERENCES**